non-reverting mutation that comprises a substitution of at least two nucleotides of a start codon. The Examiner maintained, however, that reversion of single point mutations was a well-known phenomenon, and that loss of attenuation was also a well-known problem in the art of live viral vaccines. The Examiner maintained, therefore, that one of ordinary skill would not require particular direction or specific teachings of instability to be motivated to choose a method of inactivating the VP5 gene which has a low probability of reversion to an non-attenuated form, and that inactivation methods include known methods of altering more than one nucleotide in the start codon and adding multi-frame stop codons. The Examiner considered the Mundt declaration but concluded that the observed lack of reversion is seen as the expected result, not an unexpected result and, therefore, the arguments are unconvincing and the rejection was maintained.

Applicants respectfully traverse the rejection of claims 32-39 for obviousness over the references cited. It is respectfully submitted that based on the prior art a single VP5 base pair substitution would appear to have been sufficient, as this was disclosed in the Mundt publications and would have been seen by the ordinary practitioner to be a sufficient teaching that a stable attenuated virus resulted.

As Applicants discussed in the Remarks accompanying the Amendment filed December 11, 2000, the Lewin reference relied on by the Examiner to show that the reversion to wild-type can occur reports that true reversion, which is the exact reversal of the original mutation, which Applicants discovered occurred after the publications of the Mundt references, is very rare. Lewin, in the paragraph in column 2, on page 73, beginning line 18, reports:

> "A forward mutation results from any change that inactivates a gene, whereas a back mutation must restore

function to a protein damaged by a particular forward mutation. Thus the demands for back mutation are much more specific than those for forward mutation. The rate of back mutation is correspondingly lower than that for forward mutation, particularly by a factor of [approximately] 10."

In his final paragraph Lewin states "[f]orward mutations occur at a rate of [approximately] 10^{-6} per locus per generation; back mutations are rare. Not all mutations, have an effect on the phenotype."

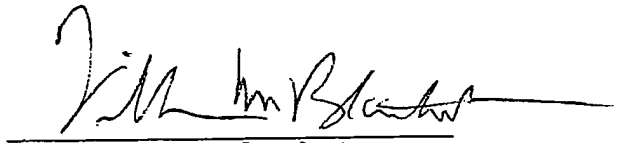
Accordingly, in view of these specific teachings by Lewin, the ordinary practitioner, although knowing that back mutations are possible, would believe them to be extremely rare and unexpected. Lewin, if anything, teaches against the likelihood of having a reversion to the point mutation in VP5.

In order to find the motivation it must be considered what the ordinary practitioner would expect in view of the cited literature. In this case, the ordinary practitioner would consider that a reversion to a specific point mutation would be extremely rare and, in view of the Mundt publications, would, if anything, find the prior art to teach a stable attenuated virus is obtained with a single VP5 point mutation. Although, theoretically, a reversion could occur, there is nothing in any of the cited literature to cause the ordinary practitioner to expect that reversion. "When obviousness is based on a particular prior art reference, there must be a showing of suggestion or motivation to modify the teachings of that reference." B.F. Goodrich Co. v. Aircraft Braking Systems Corp. 37 USPQ2d 1314, 1318 (Fed. Cir. 1996). "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under § 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so." [italics in the original] ACS Hospital Systems, Inc. v. Montefiore Hospital 221 USPQ 929,933 (Fed. Cir. 1984).

Applicants respectfully submit that the disclosure by Mundt of a single VP5 point mutation and the general teaching that there is a possibility of back mutation, but including the teaching that the back mutation should be at the rate of one tenth of 10^{-6} per locus per generation, could not possibly satisfy the requirement that there is an incentive to combine the general teaching of the rarely occurring back mutation with the existence of an attenuated virus with the single mutation, so that it would appear necessary to create an IBDV mutant by substituting at least two nucleotides within the start codon of the VP5 gene. Based on this prior art, the ordinary practitioner would believe that no advantage would be obtained by making further mutations and, of course, the efficacy of the attenuated vaccine virus could possibly be lost by this further mutation.

It is believed that claims 32-39 recite a patentable improvement in the art. Favorable consideration is solicited.

Respectfully submitted,



William M. Blackstone
Attorney for Applicants
Registration No. 29,772

Attorney Docket NO. I/97269 US
Akzo Nobel Patent Department
1300 Piccard Drive, Suite 206
Rockville, Maryland 20850-4373
Tel: (301) 948-7400
Fax: (301) 948-9751

WMB:lcf
71LUTTICKEN-RESPONSEAFTERFINAL